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Most of the early negative randomized trials of HDC in BC studied the single-cycle late-intensification approach, following conventional induction therapy. Crown and Norton (Sem Oncol 1995) hypothesized that "induction" CDC might make little cytoreductive contribution to a strategy which includes HDC, and that multiple densely sequenced cycles of HDC might be preferable. In the International Randomized Breast Cancer Dose-Intensity Study (IBDIS-I), patients received a brief phase of CDC induction, followed by tandem cycles of autograft-supported high-dose therapy (HDC), or, CDC alone, in chemotherapy-naïve MBC. Accrual failed in the aftermath of the Bezwoda disclosures, and only 110 of a planned 264 patients were enrolled. **Results:** There were 7 treatment deaths (2-CDC; 5-HDC). Complete and overall response rates (CR/OR) were significantly superior for HDC v CDC (CR-29% v 6%, OR-71% v 44%). Event-free-survival at 3 yrs was: HDC 16% versus CDC 9% (p = .0149). Currently, at a median (med) follow-up of 47 months (range 70-24), 14% of HDC and 7% of CDC pts remain event-free (34% versus 26% alive, 21% v 11% progression-free). The med duration of EFS (and OS) were: HDC 428 (961) and CDC 291 (795) days (EFS: $p = 0.019$, and for survival: $p = 0.14$). Progression–free survivals were: HDC 439, CDC 322 days ($p = .0096$). Although these data appear to conflict with the results of other studies, there were critical design differences between IBDIS and most of the other trials, which usually applied single high-dose cycles, often many months after the start of conventional chemotherapy for metastasis, as "late intensification" for patients in ongoing response to prior CDC. **Conclusion:** HDC remains a valid investigational strategy for MBC. The recent report of a second positive "minimum induction/tandem transplant" trial by Nitz et al (ASCO 2003) suggests that the breast oncology and transplant communities should come together to perform a definitive investigation of primary multi-cycle HDC, rather than initiating further studies of "traditional" single-cycle, late-intensification HDC. This approach will be tested in IBDIS-II.

STEM CELL BIOLOGY

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ALDEHYDE DEHYDROGENASE [ALDH] AND SURFACE ANTIGEN EXPRESSION DEFINE HEMATOPOEITIC STEM AND PROGENITOR CELL [HSPC] SUBSETS DIFFERENTIALLY REPRESENTED IN MOBILIZED PERIPHERAL BLOOD [PBSC], UMBILICAL CORD BLOOD [UCB], AND BONE MARROW [BM]

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Flow cytometric analysis of ALDH activity identifies HSPC in UCB, PBSC, and BM as ALDH-bright, side scatter low [ALDHbr-SSclow] populations. We used a panel of 21 monoclonal antibodies to compare the immunophenotypes of cells in ALDHbr-SSclow populations in each type of graft material. BM was obtained from normal donors; PBSC, from cancer patients or normal donors. UCB samples were processed with hetastarch or hetastarch and ficoll. Fresh samples were analyzed after erythrocyte lysis by methods optimized for each graft type. ALDHbr-SSclow cells comprised 0.5-1.1% of the total nucleated cells. We collected immunophenotype data from >3000 gated ALDHbr-SSclow cells per sample. In all three graft types, >90% of the ALDHbr-SSclow cells expressed no lineage marker characteristic of mature lymphocytes, NK cells, monocytes, or developing erythrocytes. However, the ALDHbr-SSclow population in each graft type was composed of different proportions of cells expressing surface markers associated with HSPC function. First, the proportion of primitive CD34+CD38-cells in the ALDHbr-SSclow population was considerably higher, and expression of the myeloid lineage markers CD13 and CD33 was lower, in UCB than in PBSC or BM. Second, the ALDHbr-SSclow population in UCB, but not in PBSC or BM populations, included about four times more CD7+ cells than CD3+ cells, suggesting that CD7+ lymphoid progenitors are enriched in the UCB population. Third, BM ALDHbr-SSclow cells were enriched about 50-fold for CD105, a marker associated with hematopoeitic and non-hematpoietic stem cell functions, and about 2-fold for both stem cell growth factor receptor CD117 and the early differentiation marker CD41 relative to populations from PBSC and UCB. Finally, cells expressing CD133 were about 2.5 times more frequent in PBSC than in BM or UCB. The proportion of the total population of cells expressing a given surface marker that also had the ALDHbr-SSclow phenotype varied from 88.5% of the CD34+ cells in PBSC to 1.2% of CD90+ cells in UCB. In some cases, the proportion of cells expressing a given marker that also ALDHbr-SSclow was different in different graft types. For example, 64.1% of the CD105+ cells in BM, but 0.5% of the CD105+ cells in UCB and PBSC, were ALDHbr-SSclow. Thus, ALDH expression and surface antigen expression together define new stem/progenitor cell subsets that are differentially represented in the three types of hematopoeitic graft material we analyzed.

SUPPORTIVE CARE

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PREVENTION OF CYTOMEGALOVIRUS (CMV) REACTIVATION BY STANDARD DOSE VALACYCLOVIR (VACV) AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

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In spite of the advances in the strategies against CMV reactivation and subsequent disease, including preemptive or prophylactic administration of ganciclovir, CMV disease causes significant morbidity and mortality in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT). Although ganciclovir is highly effective against CMV, its myelotoxicity is associated with secondary infection and reduced survival. In contrast, acyclovir and its prodrug VACV have a more favorable safety profile. A recent study showed a significant reduction in the incidence of CMV reactivation after allogeneic HSCT with high-dose VACV (8000 mg/day) as compared with acyclovir (Ljungman P, et al, 2002). We have examined an efficacy of standard dose VACV in the prevention of CMV reactivation after allogeneic bone marrow transplantation (BMT). Twelve CMV seropositive recipients and/or donor subjects, who underwent allogeneic BMT from an HLA-matched unrelated donor, were enrolled. Patients were conditioned with TBI- or busulfan-based myeloablative conditioning regimens. Patients received i.v. acyclovir (750 mg/dody/day) from day-3 until patients became capable of taking oral VACV. VACV was initiated at a dose of 3000 mg/day and continued until day 100. CMV reactivation was monitored by CMV antigenemia assay and real-time PCR using plasma. Thirty-five patients undergoing unrelated BMT without any prophylactic therapy against CMV were used as a comparable control. CMV reactivation was detected in 4 of 12 patients (33%) as compared with 24 of 35 (68.6%) in a control ($P<0.05$). Among the 4 patients with CMV reactivation, 2 preemptively received ganciclovir, while CMV reactivation became undetectable with VACV alone in the 2 remaining patients. No case developed CMV disease, while 14% developed CMV disease in a control (not significant). Adverse events probably due to VACV include nausea in 2 patients, and thromobocytopenia in 2 patients. These data strongly suggested that standard dose VACV could safely and effectively prevent CMV reactivation in high-risk patients undergoing allogeneic HSCT.